SYNTHESIS AND REACTIONS OF 2-(2-ARYLVINYL) PYRIMIDINES

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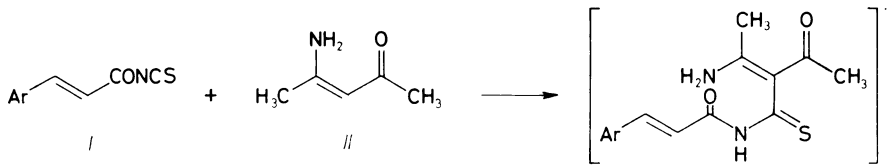
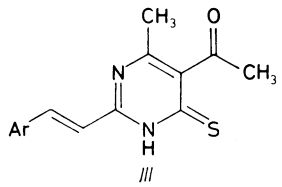
2-(2-Arylvinyl)-4-mercapto-5-acetylpyrimidines *IIIa*—*IIId* were synthesized by condensation of cinnamoyl isothiocyanates *Ia*—*Id* with 2-aminopent-2-ene-4-one *II*. The synthesis of 4-methylthio-, 4-(β-cyano)ethylthio- and 4-oxopyrimidines is also described. Compounds *IV* reacted with hydrazine hydrate to yield the corresponding pyrazolopyrimidine.

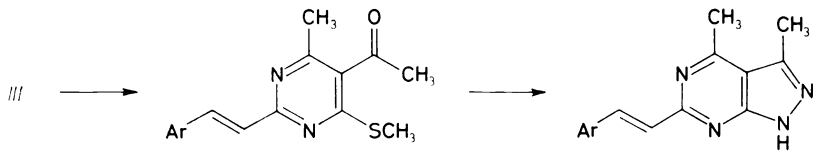
As a part of a programme directed towards the synthesis of new suitably functionalized condensed pyrimidines of potential biological activity we needed 2-(2-arylvinyl)--4-mercapto-5-acetylpyrimidine derivatives *III* as starting materials. Pyrimidines with such functionalities are potential starting compounds for preparation of condensed pyrimidine derivatives, some of which have been described[1-4] together with their biological activity[1].

In this communication we wish to report a simple one-step synthesis of 2-(2-arylvinyl)-4-mercapto-5-acetylpyrimidines *IIIa*—*IIId* from the corresponding cinnamoyl isothiocyanates *Ia*—*Id* and 2-aminopent-2-en-4-one *II*. An earlier paper[5] reported a two-step synthesis of compound *IIIa* in which the corresponding intermediate A was isolated in the first step (Scheme 1). Attempts to synthesize compound *IIIa* by this procedure resulted in very low yield (40%). We have found that the condensation of cinnamoyl isothiocyanates *Ia*—*Id* with *II* in refluxing dioxane afford the corresponding pyrimidines *IIIa*—*IIId* in good yield. Higher yields of 4-thiopyrimidines were obtained when the cinnamoyl isothiocyanates contained an electron withdrawing group. On the other hand, the condensation with *p*-methoxycinnamoyl isothiocyanate gave a very poor yield of *IIId*. These facts reflected the requirement of an electron deficient carbonyl to facilitate the ring closure and subsequent dehydration. Methylation of compounds *IIIa* and *IIIb* with methyl iodide in an alkaline medium yields the corresponding 4-methylthiopyrimidines *IVa* and *IVb*, respectively, and none of the possible N-methyl derivatives. The structures of compounds *IVa* and *IVb* were established by the fact that they react with hydrazine hydrate to give the corresponding pyrazolo[3,4-*d*]pyrimidines *Va* and *Vb* and methyl mercaptane. Compounds *IIIa* and *IIIb* undergo cyanoethylation when heated with acrylonitrile in absolute ethanol under basic conditions to yield the corresponding 4-(β--cyanoethyl)thiopyrimidines *VIa*, *VIb* and none of the possible isomeric N-cyano-



In formulae *I* and *III*: *a*, Ar = C_6H_5 *b*, Ar = *p*-ClC_6H_4
c, Ar = *p*-$NO_2C_6H_4$ *d*, Ar = *p*-$CH_3OC_6H_4$

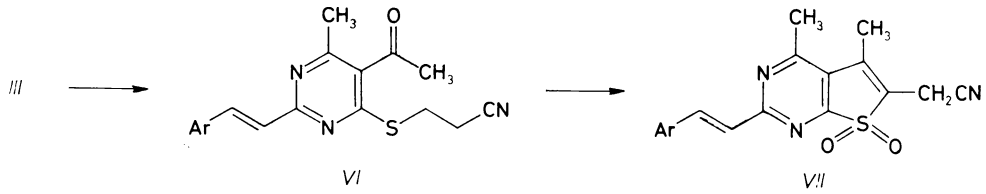




In formulae *IV* and *V*: *a*, Ar = C_6H_5 *b*, Ar = *p*-ClC_6H_4

SCHEME 1

ethyl derivatives (Scheme 2). The structure of the products *VIa* and *VIb* is inferred from the fact that their UV spectra are closely similar to those of methylthio deriva-

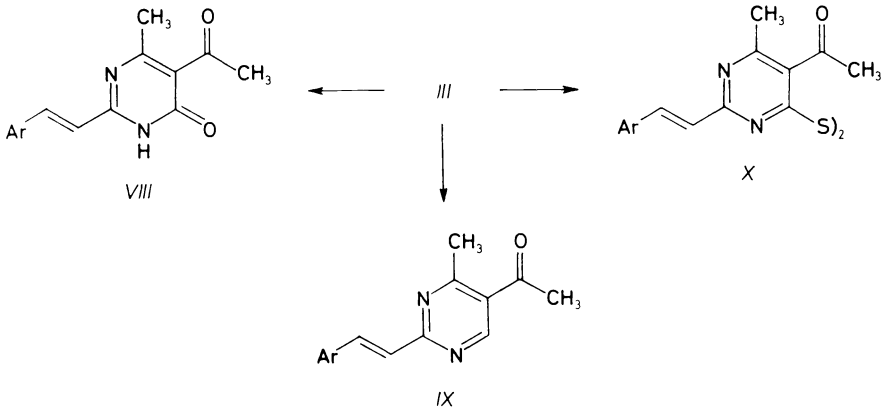


In formulae *VI* and *VII*: *a*, Ar = C_6H_5 *b*, Ar = *p*-ClC_6H_4

SCHEME 2

tives *IVa* and *IVb*. Furthermore, treatment of the products *VIa* and *VIb* with 40% sodium hydroxide solution resulted in recovery of the starting precursors *IIIa* and *IIIb*, respectively, but not of the corresponding carboxylic acids as reported for some N-cyanoethyl derivatives[6,7]. Oxidation of compounds *VIa* and *VIb* with potassium permanganate in sulfuric acid provided the thieno[2,3-*d*]pyrimidine 7,7-dioxide *VII*.

Reaction of compounds *IIIa* and *IIIb* with hydrogen peroxide in the presence of NaOH provided the corresponding oxo derivatives *VIIIa* and *VIIIb*, while in the presence of acetic acid desulfurization took place under formation of pyrimidines *IXa* and *IXb* (ref.[8]). Oxidation of pyrimidines *IIIa* and *IIIb* with iodine in acetic acid gave the respective disulfides *Xa* and *Xb* (Scheme 3).



In formulae *VIII*–*X*: *a*, Ar = C_6H_5 *b*, Ar = *p*-ClC_6H_4

SCHEME 3

EXPERIMENTAL

All melting points (Table I) are uncorrected. Microanalyses (Table I) were carried out at the Microanalytical Centre, Cairo University. ^{1}H NMR spectra were recorded on a Varian HA 100 (100 MHz) instrument in $CDCl_3$ using TMS as internal reference. Mass spectra were recorded in a Finningan GC/MS Model 4023 mass spectrometer. Ultraviolet spectra were obtained in a Unicam SP 1750 spectrometer.

2-(2-Arylvinyl)-4-mercapto-6-methyl-5-acetylpyrimidines *IIIa*–*IIId*

A mixture of cinnamoyl isothiocyanate *Ia*–*Id* (0·1 mol, prepared from ammonium thiocyanate (0·12 mol) and the substituted cinnamoyl chloride[9] (0·1 mol)) and compound *II* (0·1 mol) in dioxane was refluxed for 2 hours. The solid separated after cooling was filtered and crystallized from ethanol to yield yellow crystals of *IIIa*–*IIId*. ^{1}H NMR spectra: *IIIa*: 2·5 s, 3 H (CH_3); 3·0 s, 3 H (CH_3); 7·1–8·0 m, 7 H (ArH + CH=CH); 10·0 s, 1 H (NH). *IIIc*: 2·65 s, 3 H

TABLE I

Characteristics of prepared compounds

Compound	M.p., °C (Yield, %)	Formula	Calculated/Found				
			% C	% H	% Cl	% N	% S
IIIa	242—243 (70)	$C_{15}H_{14}ON_2S$	66·62 66·10	5·22 5·30		10·36 10·30	11·86 11·80
IIIb	217—218 (65)	$C_{15}H_{13}ClON_2S$	59·08 59·00	4·30 4·20	11·63 11·60	9·19 9·10	10·52 10·50
IIIc	240—242 (80)	$C_{15}H_{13}O_3N_3S$	57·11 57·00	4·15 4·10		13·33 13·30	10·17 10·10
IIId	188—189 (45)	$C_{16}H_{16}O_2N_2S$	63·95 63·90	5·37 5·30		9·33 9·30	10·67 10·60
IVa	71—72 (70)	$C_{16}H_{16}ON_2S$	67·57 67·00	5·67 5·30		9·85 9·50	11·28 11·00
IVb	83—85 (65)	$C_{16}H_{15}ClON_2S$	60·25 60·40	4·74 4·50	11·12 11·50	8·78 8·30	10·06 10·60
Va	280 (88)	$C_{15}H_{14}N_4$	71·96 71·80	5·64 5·70		22·39 22·40	
Vb	186—188 (92)	$C_{15}H_{13}ClN_4$	63·25 63·20	4·60 4·60	12·45 12·50	19·68 19·70	
VIa	102—103 (70)	$C_{18}H_{17}ON_3S$	66·83 66·70	5·30 5·00		12·99 12·40	9·91 9·40
VIb	113—115 (72)	$C_{18}H_{16}ClON_3S$	60·04 60·70	4·50 4·30	9·91 9·50	11·74 11·20	8·96 8·60
VIIa	214—216 (50)	$C_{18}H_{15}O_2N_3S$	64·07 64·00	4·48 4·20		12·45 12·20	9·50 9·50
VIIb	210—212 (45)	$C_{18}H_{14}ClO_2N_3S$	58·12 58·00	3·79 3·60	9·54 9·50	11·30 11·20	8·62 8·60
VIIIa	225—228 (50)	$C_{15}H_{14}O_2N_2$	70·83 70·80	5·55 5·50		11·02 11·00	
VIIIb	232—234 (45)	$C_{15}H_{13}ClO_2N_2$	62·37 62·40	4·54 4·50	12·28 12·30	9·70 9·80	
IXa	215—216 (40)	$C_{15}H_{14}ON_2$	75·59 75·60	5·92 5·90		11·76 11·20	
IXb	223—224 (45)	$C_{15}H_{13}ClON_2$	66·04 66·00	4·80 4·80	13·00 12·90	10·27 10·20	
Xa	176—177 (65)	$C_{30}H_{26}O_2N_4S_2$	66·04 66·80	4·80 4·80		10·27 10·40	13·00 12·60
Xb	182—183 (60)	$C_{30}H_{24}Cl_2O_2N_4S_2$	59·28 59·30	3·98 3·90	11·67 11·60	9·22 9·10	10·55 10·00

(CH_3); 3·1 s, 3 H (CH_3); 7·1–8·0 m, 6 H (ArH + CH=CH); 10·0 s, 1 H (NH). *IIId*: 2·50 s, 3 H (CH_3); 3·0 s, 3 H (CH_3); 4·1 s, 3 H (CH_3); 7·0–8·0 m, 6 H (ArH + CH=CH); 10·0 s, 1 H (NH). IR spectrum (KBr, cm^{-1}): *IIIb*: 3 200–2 300 (br, NH); 1 665 (CO); 970–980 (s, CH=CH *trans*). Mass spectrum: *IIIa*: 270 (M^+); *IIIb*: 303 (M^+). UV spectrum (methanol, λ_{max}, nm, ε): *IIIb*: 370 (4·54).

2-(2-Arylvinyl)-4-methylthio-6-methyl-5-acetylpyrimidines *IVa* and *IVb*

A mixture of pyrimidine *IIIa* or *IIIb* (0·01 mol), methyl iodide (0·015 mol), water (25 ml) and sodium hydroxide (0·01 mol) was stirred for 2 hours. The solid that separated was filtered and crystallized from aqueous methanol to yield colourless crystals of *IVa* or *IVb*. IR spectrum (KBr, cm^{-1}): *IVa*: 1 670 (m, CO); 970 (s, CH=CH *trans*). UV spectrum (methanol, λ_{max}, nm, ε): *IVa*: 314 (28·40), 230 (11·44).

Pyrazolo[3,4-*d*]pyrimidines *Va* and *Vb*

A mixture of compound *IVa* or *IVb* (0·01 mol), hydrazine hydrate (0·02 mol) and ethanol (20 ml) was heated under reflux for 2 hours. After cooling, the resulting precipitate was collected and crystallized from ethanol to give yellow crystals of *Va* or *Vb*. ^{1}H NMR spectra: *Va*: 2·65 s, 3 H (CH_3); 3·1 s, 3 H (CH_3); 7·0–8·0 m, 7 H (ArH + CH=CH); 9·5 s, 1 H (NH). *Vb*: 2·65 s, 3 H (CH_3); 3·1 s, 3 H (CH_3); 7·0–8·0 m, 6 H (ArH + CH=CH); 9·5 s, 1 H (NH).

2-(2-Arylvinyl)-4-(β-cyanoethylthio)-6-methyl-5-acetylpyrimidines *VIa* and *VIb*

A mixture of pyrimidine *IIIa* or *IIIb* (0·01 mol), acrylonitrile (0·15 mol), water (25 ml) and sodium carbonate (0·01 mol) was stirred for 6 hours. The solid that separated was filtered, washed several times with water and crystallized from ethanol to yield colourless crystals of *VIa* or *VIb*. ^{1}H NMR spectrum: *VIb*: 2·5 s, 3 H (CH_3); 2·7 s, 3 H (CH_3); 3·0 t, 2 H (SCH_2CH_2CN, J = 6); 3·7 t, 2 H (SCH_2CH_2CN, J = 6); 7·1–8·0 m, 6 H (ArH + CH=CH). IR spectrum (KBr, cm^{-1}): *VIa*: 2 240 (w, CN); 1 670 (m, CO); 970 (s, CH=CH *trans*). *VIb*: 2 240 (w, CN); 1 670 (m, CO); 970 (s, CH=CH *trans*). UV spectrum (methanol, λ_{max}, nm, ε): *VIa*: 314 (19·83), 230 (8·53); *VIb*: 314 (29·38), 230 (8·53). Mass spectrum: *VIa*: 323 (M^+); *VIb*: 359 (M^+).

Action of Sodium Hydroxide on Compounds *VIa* and *VIb*

A suspension of compound *VIa* or *VIb* (0·01 mol) in aqueous sodium hydroxide solution (25%, 20 ml) was heated under reflux for 8 hours. The obtained clear solution was cooled in an ice bath and acidified with concentrated hydrochloric acid to slightly acidic reaction. The solid obtained was filtered, washed several times with water and crystallized from ethanol. The melting points and M^+ data of this compound were compared with those of an authentic sample of compound *III* and were found to be identical.

2-(2-Arylvinyl)-6-cyanomethyl-4,5-dimethylthieno [2,3-*d*]pyrimidine 7,7-Dioxides *VIIa* and *VIIb*

A solution of compound *VIa* or *VIb* (0·01 mol) in chloroform (10 ml) and sulfuric acid (2 ml) was cooled to 0°C and then potassium permanganate (0·1 mol) was added slowly in portions. The solution was set aside at room temperature, made alkaline, decolourized with acetone and extracted with chloroform. After evaporation to dryness the residue was crystallized from ethanol to give colourless crystals of *VIIa* or *VIIb*. IR spectrum (KBr, cm^{-1}): 2 240 (w, CN); 970 (s, CH=CH *trans*).

2-(2-Arylvinyl)-6-methyl-5-acetyl-3*H*-pyrimidine-4-ones *VIIIa* and *VIIIb*

A mixture of *IIIa* or *IIIb* (0·01 mol), hydrogen peroxide (30 ml, 30%) and acetic acid (20 ml) was shaken for 5 minutes. The solution was then boiled for 3 minutes. After cooling with ice water and scratching, the crystalline precipitate was collected and recrystallized from acetic acid to give pale yellow crystals of *VIIIa* or *VIIIb*. ^{1}H NMR spectrum: *VIIIb*: 2·4 s, 3 H (CH_3); 2·6 s, 3 H (CH_3); 6·85—8·0 m, 6 H (ArH + CH=CH); 12·7 br, 1 H (NH). IR spectrum (KBr, cm^{-1}): *VIIIa*: 3 100—2 500 (br, NH); 1 680—1 020 (br, CO); 975 (s, CH=CH *trans*). *VIIIb*: 3 100—2 500 (br, NH); 1 680—1 625 (br, CO), 975 (s, CH=CH *trans*).

2-(2-Arylvinyl)-6-methyl-5-acetylpyrimidines *IXa* and *IXb*

A mixture of *IIIa* or *IIIb* (0·01 mol), hydrogen peroxide (30 ml, 30%) and acetic acid (20 ml) was shaken for 5 minutes. After cooling with ice water and scratching, the crystalline precipitate was collected and recrystallized from acetic acid to give pale yellow crystals of *IXa* or *IXb*. ^{1}H NMR spectrum: *IXb*: 2·5 s, 3 H (CH_3); 2·6 s, 3 H (CH_3); 6·45—7·75 m, 7 H (ArH + CH=CH + pyrimidine H). IR spectrum (KBr, cm^{-1}): 1 670 (s, CO); 980 (s, CH=CH *trans*). *IXb*: 1 670 (s, CO); 980 (s, CH=CH *trans*).

(6-Methyl-2-styryl-5-acetylpyrimidin-4-yl)disulfides *Xa* and *Xb*

To a solution of compound *IIIa* or *IIIb* (0·01 mol) in acetic acid was added iodine (0·01 mol) with stirring. The obtained yellow crystals were collected by filtration and recrystallized to give yellow crystals of *Xa* or *Xb*. ^{1}H NMR spectrum: *Xb*: 2·4 s, 6 H (2 × CH_3); 2·6 s, 6 H (2× CH_3); 6·45—7·70 m, 12 H (ArH + CH=CH). IR spectrum (KBr, cm^{-1}): *Xa*: 1 670 (s, CO); 975 (s, CH=CH *trans*). *Xb*: 1 670 (s, CO); 980 (s, CH=CH *trans*).

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